36. (New) A method according to claim 35, wherein expression of said SXR polypeptide activates in the transgenic mouse a response to natural and synthetic steroid hormones to which a wild type mouse does not respond.

37. (New) A method according to claim 35, wherein the promoter/enhancer is an inducible promoter/enhancer.

38. (New) A method according to claim 35, wherein the promoter/enhancer is a constitutively active promoter/enhancer. --

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REMARKS

Courtesies extended to Applicants' representative Stephen E. Reiter in the personal interview held on August 2, 2000 and to Applicants' representatives Stephen E. Reiter and Stanley H. Kim in the personal interview held on November 29, 2000, are acknowledged with appreciation.

The present invention provides transgenic mice whose genome contains a transgene comprising a gene encoding a human steroid and xenobiotic receptor (SXR) polypeptide operably linked to a promoter/enhancer, wherein said SXR polypeptide is a member of the steroid/thyroid hormone superfamily and forms a heterodimer with retinoid X receptor, binds to a direct or inverted repeat response element based on defined six nucleotide half sites, and activates transcription in response to a wide variety of natural and synthetic steroid hormones. Invention transgenic mice express SXR polypeptide in at least one of the liver and intestine. In one aspect of the invention, inducible expression of SXR polypeptide activates in the transgenic mouse a response to natural and synthetic steroid hormones to which a wild type mouse does not respond. In another aspect of the invention, constitutive expression of SXR polypeptide results in hepatomegaly and growth retardation in the transgenic mouse as compared to a wild type mouse.

In another embodiment, the invention provides transgenic knock-out mice whose genome comprises a disruption in an endogenous SXR polypeptide gene, wherein said disruption prevents production of a functional SXR polypeptide and results in the transgenic knockout mouse exhibiting decreased response to natural and synthetic steroid hormones as compared to a wild-type mouse.

In another embodiment, the invention provides methods for producing transgenic mice by injecting a one-cell mouse zygote with a transgene comprising a gene encoding a human steroid and xenobiotic receptor (SXR) polypeptide operably linked to an inducible or a constitutive active promoter/enhancer, and obtaining from the zygote a transgenic mouse that expresses SXR polypeptide in the liver, thereby activating in the transgenic mouse a response to the natural and synthetic steroid hormones to which a wild type mouse does not respond.

Claims 6, 8 and 10-12 were pending before this Response. By the present communication, claims 6, 8, 10-12 are canceled and new claims 13-38 are added. The new claims add no new matter as they are fully supported by the Specification and original claims. Claims 13-38 are currently pending.

The Sequence Listing

Responsive to the Notice To Comply With Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures received herein, Applicants submit under separate cover a Sequence Listing, a copy of the sequence information in computer readable form, and a Statement Under 37 C.F.R. § 1.821(f) and (g) that the enclosed Sequence Listing includes no new matter.

The Requirement for Formal Drawings

Applicants acknowledge that the application has been filed with informal drawings and will comply with the requirement to submit formal drawings upon receipt of a Notice of Allowance in this application.

The Rejection under 35 U.S.C. § 101

Applicants respectfully traverse the rejection of claims 6 and 8 for allegedly containing non-statutory subject matter because the claims would encompass a transgenic human being. By the present communication, claims 6 and 8 are canceled and new claims 13-24 are specifically directed to "transgenic mice." As a mouse is a non-human animal, and hence constitutes statutory subject matter under 35 U.S.C. § 101, Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection under 35 U.S.C. § 112, First Paragraph

Applicants respectfully traverse the rejection of claims 6, 8, and 10-12 under 35 U.S.C. § 112, First Paragraph, for allegedly containing subject matter not enabled by the teaching of the Specification. The rejection has been rendered moot with respect to claims 6, 8, and 10-12 by the cancellation thereof pursuant to the present communication. New claims 13-24 fully satisfy the requirements of U.S.C. § 112, First Paragraph, by requiring that the transgenic animal have a genome that contains a transgene comprising a gene encoding a human steroid and xenobiotic receptor (SXR) polypeptide operably linked to an inducible or constitutively active promoter/enhancer, "wherein said SXR polypeptide forms a heterodimer with retinoid X receptor, binds to a direct or inverted repeat response element based on a defined half site . . . , and constitutively activates transcription through response elements found in steroid inducible P450 genes in response to a wide variety of natural and synthetic steroid hormones, including at least compounds that induce catabolic enzymes, steroid receptor agonists and antagonists, and bioactive dietary compounds, and wherein said polypeptide is detectably expressed in the liver and the intestine" (emphasis added).

Indeed, as acknowledged by the Examiner, the Specification provides enablement for at least two transgenic mice whose production is fully described therein (Office Action, pages 3 and 4). In addition, as discussed at the personal interviews, Applicants were first to enable production of invention transgenic mice, which is deminstrated by the exemplary transgenic mice described in the specification. However, while new claims 13-38 are presented by this communication to expedite prosecution and reduce the issues herein, their submission should in no way be construed as acquiescence in the rejection of the original claims as allegedly being unduly broad for failure to provide an enabling description in the Specification.

In view of the above amendments and remarks, Applicants respectfully submit that new claims 13-24 are fully enabled under 35 U.S.C. § 112, First Paragraph. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection under 35 U.S.C. § 112, Second Paragraph

A. Claims 6, 8 and 10-12 are rejected under 35 U.S.C. § 112, Second Paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to those skilled in the art that the inventors had possession of the claimed invention. This rejection is traversed and has been rendered moot with respect to claims 6, 8, and 10-12 by the cancellation thereof pursuant to the current communication. This rejection is not applicable to new claims 13-24, which are drawn to embodiments of the invention wherein the transgenic animal is a transgenic mouse having a particular described phenotype.

B. Claims 6, 8 and 10-12 are rejected under 35 U.S.C. § 112, Second Paragraph, for allegedly being indefinite. This rejection is traversed and has been rendered moot with respect to claims 6, 8, and 10-12 by the cancellation thereof pursuant to the current communication. New claims 13-24 are not subject to this rejection as these claims are free of any indefiniteness for the following reasons.

Applicants respectfully disagree with the Examiner's assertion that it is allegedly unclear in claims 6, 8, 10 and 12, which response elements are bound by the receptor polypeptide or whether the receptor polypeptide binds as a heterodimer with RXR to activate transcription (Office Action, page 13). New claims 13, 18 and 21 all clearly require that the receptor polypeptide forms a heterodimer with RXR and that the heterodimer binds to the response element to activate transcription.

Applicants respectfully disagree with the Examiner's assertion that the phrase "or functional fragment," as used in claims 6, 8 and 12, allegedly lacks clarity because "the specification is silent with details of specific fragments of the encoded polypeptide which are functional or methods to create, identify and/or assay for functional fragments of the recited SEQ ID Nos" (Office Action, pages 13-14). The Specification discloses an assay for determining a functional fragment of the invention receptor polypeptide by hybridizing test DNA with a labeled single stranded nucleic acid probe comprising at least 20 contiguous bases in length having substantially the same sequence as any 20 or more contiguous bases selected from bases 1 - 2068, inclusive, of the DNA illustrated in SEQ ID NO:1, or the complement thereof, under high stringency conditions, and selecting as invention SXR receptors, or functional fragments thereof, those sequences which hybridize to the probe (Specification, page 26, line 26 to page 27, line 3 and lines 7-18). Thus, Applicants respectfully submit that the phrase "or functional fragment," as the term is employed with respect to invention polypeptide receptors, is clearly described in the Specification. However, to expedite prosecution and reduce the issues, the new claims submitted herewith omit the phrase "functional fragment thereof," rendering the rejection inapplicable as to these claims.

Applicants respectfully disagree with the Examiner's assertion that the phrase "prominently expressed," as the phrase is employed with respect to invention polypeptide receptors in claims 6 and 8, is allegedly unclear. Applicants respectfully submit that the Specification describes (page 36, lines 18-24) the prominence of the receptor in liver and intestine. Thus the phrase "prominently expressed," as the term is employed with respect to invention polypeptide receptors, is clearly described in the Specification. However, to expedite prosecution and reduce

the issues, in the new claims, the term "prominently" is avoided. Instead, invention SXR receptors are required to be "detectably expressed" in the liver and intestine, thus clarifying the metes and bounds of SXR expression in the new claims.

Applicants respectfully disagree with the Examiner's assertion that the phrase "is characterized by," as employed with respect to invention polypeptide receptors in claims 6 and 8, is allegedly unclear because the phrase "makes the receptor polypeptide produced read as a product by process possessing the recited embodiments" (Office Action, page 14). Applicants respectfully submit that the extreme reading of the claim language asserted by the Examiner is unreasonable because the Specification discloses that all four of the characterizing attributes are present in invention polypeptide receptors. However, to reduce the issues, the new claims avoid the phrase "is characterized by" and instead (following suggested language of the Examiner) require invention SXR receptors to exhibit a finite series of attributes (i.e., "forms" a heterodimer with RXR and "binds" to a response element as a heterodimer, "activates" transcription and "is" detectably expressed in liver and intestine). Thus, Applicants respectfully submit that new claims 13, 18 and 21 clearly recite the four attributes required of invention SXR receptors.

Applicants respectfully disagree with the Examiner's assertion that the phrase "transgenic animal expressing a receptor polypeptide" as employed in claim 6 with regard to invention polypeptide receptors allegedly does not indicate whether the receptor polypeptide is the product of the transgene or the receptor polypeptide is the product of an the endogenous gene (Office Action, page 14). To reduce the issues, new claim 16 clearly requires the genome of the invention knock-out mouse to contain "a homozygous disruption in an endogenous SXR polypeptide gene." Thus, Applicants respectfully submit that the instance of indefiniteness alleged by the Examiner in original claim 6 is not found in new claim 16.

Applicants respectfully disagree with the Examiner's assertion that the term "cell" as employed in original claim 11 with respect to invention polypeptide receptors is allegedly unclear due to lack of antecedent basis for "cell" in the preamble of the claim. By the present communication, claim 11 is canceled without prejudice. New claim 14 avoids reference to a "cell"

and requires instead a "transgenic mouse" transformed with a vector comprising a promoter that is operable in "said mouse," thus providing antecedent basis for the term "said mouse" in the preamble of the claim. Thus, Applicants respectfully submit that new claim 14 meets all requirements for definiteness under 35 U.S.C. § 112, Second Paragraph.

Applicants respectfully disagree with the Examiner's assertion that the phrase "express substantially no steroid or xenobiotic receptor" as employed in original claim 12 with respect to invention polypeptide receptors allegedly lacks clarity regarding whether "expression is decreased or completely ablated in the whole animal or only in some tissues, or if the animal is still capable of expressing the receptor, [whether] the proper stimulation is present but no longer has constitutive levels of expression" (Office Action, page 15). By the present communication, original claim 12 is canceled and replaced by new claim 16, which requires a "transgenic knock-out mouse whose genome contains a homozygous disruption in an endogenous SXR polypeptide gene." Thus, production of a functional endogenous SXR receptor polypeptide in the knockout mouse is prevented. As a result, an invention knock-out mouse is required to exhibit the phenotype of "decreased response to natural and synthetic steroids as compared to a wild-type mouse." In view of the clear requirement that a functional endogenous SXR receptor polypeptide is not produced in the invention knock-out mouse, as defined by new claim 16, Applicant respectfully submits that any perceived lack of clarity in original claim 12 is avoided in new claim 16.

In view of the above amendments and remarks, reconsideration and favorable action on claims 13-38 are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: 12/4/00

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